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Risk Assessment for P-89-867

I. SUMMARY

P-89-867 was submitted by [redacted] for the manufacture of [redacted] at a maximum rate of [redacted] kg/y. The PMN substance will be marketed primarily as a replacement for [redacted] a [redacted] flame retardant receiving attention for its generation of [redacted] during plastics processing.

Environmental fate of the PMN substance is very uncertain; rapid photolysis in air and water is expected.

[redacted] is the primary analog for the health risk case. Use of no personal protective equipment by workers was assumed. Based on a developmental toxicity LOAEL, and a subchronic toxicity NOEL and RfD for [redacted] margins of exposure for worker exposures for one manufacturing, two processing, and two use scenarios are inadequate. The cancer risks for processing workers are ~~unacceptably high~~ significant. Health risks for other workers and for the general public are not expected to exceed the HERD criteria for significance of risk. Based on a predicted (QSAR) LC_{50} for fish for a possible phenolic degradation product-[redacted] the concentration of concern for aquatic toxicity has been set at 0.1 ppb; assuming that all of the PMN substance released to water becomes available in the water column as this phenolic species, the COC would be exceeded on [redacted] d/y at [redacted] sites for the non-consumer textile and adhesives, and miscellaneous plastics use ([redacted] of the production volume, when combined).

The following testing, with some modification relative to standard options for such tests, has been recommended: (a) Health effects - teratology study, 90-day subchronic toxicity study, and possibly a two-year cancer bioassay pending results of the subchronic study. (b) Environmental fate - fate determination under conditions of photolysis in water and in air, and under environmentally realistic conditions. (c) Environmental effects - bioaccumulation in fish and oysters, 60-day fish test, chronic algal test, chronic daphnid test, tadpole/sediment subchronic test, chironamid sediment invertebrate test, and possibly further aquatic testing pending results of environmental fate testing.

[redacted]

II. INTRODUCTION

P-89-867 was submitted for decabromodiphenylethane ([redacted] expects to manufacture the PMN substance at a maximum rate of [redacted] kg/year, following a first-year maximum of [redacted] kg.

The PMN substance is a solid with the following physical-chemical attributes: molecular weight, [redacted] melting point, [redacted]°C; water-solubility, 20 ppb[1]. The calculated[2] octanol/water partition coefficient, logP, for [redacted] is 11.1; based on analogs, logP has been estimated as *5.5[3]. The following [redacted] are present as impurities in the PMN substance: [redacted] and congeners with <8 bromines at <1%.

The primary target market for the PMN substance is flame retardants for plastics. Brominated flame retardants commonly used in plastics include the following: deca-, octa-, and pentabromodiphenyloxides; brominated styrenes; and tetrabromobisphenol A. [redacted] and [redacted] Corporation are the two largest companies manufacturing brominated flame retardants; each supplies half of the [redacted] market[4].

[redacted] is receiving attention for its generation of polybrominated dibenzofurans and dibenzodioxins at temperatures achieved during processing of certain plastics in which it is used.[5] The primary use of the PMN substance would be as a substitute for [redacted] [redacted] claims that, compared to other flame retardants, the PMN substance imparts greater UV light stability to plastics and textiles. (Ref: Economics Report.) The PMN substance would not generate dibenzofurans or dibenzodioxins.[6]

The following toxicity test results were included in the PMN: rabbit eye irritation, non-irritant; rabbit dermal irritation, non-irritant; Ames mutagenicity with and without activation, negative; rat oral LD_{50} >5000 mg/kg; rabbit dermal LD_{50} >2000 mg/kg. For the PMN substance itself, the SAT expressed high concern for health and low concern for environmental effects;

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[1]Measured by submitter.

[2]CLOGP 3.3

[3]Chemistry Report

[redacted] accounts for 60% of the non-reactive brominated flame retardants market. (Ref: Economics Report.) The economist has estimated that the maximum production volume stated in the PMN represents capture of 3% of the current brominated flame retardants market.

[5]Brominated Flame Retardants project, Dioxins/Furans Test Rule project, EPCRA (SARA Title III, Section 313) petition #P-89-005.

[6]Chemistry Report.

and for the lesser-brominated species expected from photolysis (in air)[7], high concern for the environmental effects.

At a HERD analog meeting, [redacted] was regarded as a suitable analog for toxicity assessment purposes. No significant distinction between reactivity of the [redacted] linkages joining the [redacted] groups has been identified; cleavage is not expected to occur metabolically or environmentally for either of the linkages. Polybrominated biphenyls (PBBs) have been regarded as less appropriate than [redacted] as analogs for the PMN substance. This is based upon a theory that planarity and conjugation throughout the molecule are significant aspects of the mechanism of toxicity production by [redacted].[8,9]

[redacted] submitted a petition to delist [redacted] from the list of toxic materials under EPCRA. The hazard focus for P-89-867 is a consequence of preparation of the HERD response to that petition. The risks presented arise from potential for developmental and chronic/subchronic toxicity, oncogenicity, and aquatic toxicity of the parent compounds and/or possible photolysis products. (See Figure 1 for chemical structures.)

Toxicity of the possible [redacted] and ether degradation products has not been addressed. These compounds are expected to be less toxic and less carcinogenic than [redacted]. This conclusion is based on SAR and a perspective that [redacted] is the most potent toxicant and carcinogen known; by comparison, therefore, anything expected to behave differently is expected to be less potent. (Refs: Personal communications of D. Lai, L. Keifer; 9/11/89.) Data is unavailable to compare the hazards and risks posed by these possible pyrolysis products to those posed by [redacted] arising from pyrolysis of [redacted] (Refs: Personal communications of J. Seed, D. Lai, L. Keifer; 9/11/89.)

III. ENVIRONMENTAL FATE

The PMN substance is expected to degrade readily in air and water in the presence of sunlight. Subjects of uncertainty regarding fate of the PMN substance in the environment include the following: (1) rates and products of photodegradation in air and water; (2) longevity of the degradation

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[7]See section III, Environmental Fate.

[8]Personal communication of D. Lai, 8/89.

[9]The PBBs are planar, a constraint consistent with maintaining conjugation over the entire molecule. P-89-867 and [redacted] are non-planar molecules; because the phenyl rings are isolated from one another with respect to conjugation, rotation about the bonds between rings is not energetically unfavorable.

products[10]; (3) influence of sediment, suspended solids, soil surfaces, and particulates in air on rates and paths of photodegradation; (4) amounts of PMN substance and degradation products reaching water from manufacturing emissions to air. Primary chemical species expected appear in Table 1 below; see Figure 1 for chemical structures.

Table 1: Primary degradation products expected for P-89-867

Route	Degradation products	Reference
Photolysis: Absence of water	[redacted]	Chemistry Report
Air	[redacted]	Exposure Report
Presence of water	[redacted]	Chemistry Report
	[redacted]	Exposure Report
Pyrolysis in absence of water	[redacted]	Chemistry Report

While it is agreed that photolysis in water will generate phenolic derivatives, estimates of the degree of hydroxylation, relative abundance, and longevity of the phenolic derivatives vary. According to one scenario, the phenolic species with one or two Br atoms replaced by OH groups are expected to last 1-2 days in the environment before further degradation (photolysis and biodegradation).[11]

The most environmentally-relevant route of degradation in air remains a subject of disagreement and uncertainty.

The parent compound and the [redacted] are expected to sorb very strongly to sludge, soil, and sediment. Negligible migration from

[10]According to the Chemistry Report, degradation of the phenols produced will proceed rapidly due to increased UV absorption.

[11]Personal communication of A. Leifer, 8/22/89.

landfills to groundwater is expected. In the absence of sunlight, the PMN substance is expected to be persistent, with ultimate degradation requiring longer than months[12].

IV. HAZARD

The health and environmental effects assessments for the parent compound and the [redacted] are based on reports prepared for the petition to delist [redacted] from EPCRA. Toxicity of the phenolic degradation products is covered by report for the environmental effects; and by personal communication for the health effects.

The lowest concentrations at which adverse effects have been observed are discussed below. Table 2 provides a summary of toxicity values found for the ether analogs; Table 3 describes the studies and adverse effects. Refer to Table 3 for citations with a reference number containing a T, e.g., 14T. The observation of toxicity appears to be dependent upon impurities present[13], test animals chosen, and parameters examined and reported as reflective of adverse effects. Some of the variety in the tests conducted is noted in Table 3.

Absorption, Metabolism, and Excretion

Absorption: Unless it is presented as fine particles[14], absorption of the PMN substance through the skin is not expected; this is based on a generalization for high-melting-point solids. Estimated absorption from the GI tract is 1-10%, based on analogy to a dietary study of [redacted] in Fisher 344 rats. Absorption from the lung is regarded as similar to that from the GI tract. Absorption of [redacted] (e.g.,

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[12]At the HERD Disposition meeting, J.V. Nabholz (Environmental Effects Branch/HERD) proposed the following as a realistic environmental fate scenario: Ultraviolet wavelengths (from sunlight) penetrate only the upper few centimeters of water; photolysis is not expected beyond reach of UV light. The PMN substance entering the aqueous environment adsorbs to particulate matter (or is adsorbed before entering the water), resides in the sediment, and acts as a long-term source of [redacted] for possible photolysis when sediment is disturbed.

[13]Note that the technical grade [redacted] is a mixture containing substantial amounts (e.g., 21%) of [redacted]; and commercial grade [redacted] ([redacted] may contain substantial amounts (e.g., 45%) of [redacted]

[14]Diameter < 1 micron. (Ref: Personal communication of L. Keifer, 9/6/89.)

[redacted] is expected to be greater than that for the fully-brominated compound.[15] Absorption of the phenolic derivatives is expected to be slightly higher than that for the parent compound; this is based on an expectation of slightly inceased water solubility for the phenolic compounds.[16]

Metabolism: Some debromination may occur metabolically to yield [redacted] or phenolic derivatives.

Excretion: Excretion is expected in the bile, primarily, with lesser amounts in the urine; some accumulation in tissue is possible. These conclusions are based on analogy to [redacted] metabolism and excretion.

Developmental/reproductive toxicity

Based on animal test data for [redacted] and [redacted] is expected to cause developmental toxicity, and the [redacted] are expected to cause developmental and maternal toxicity in humans. The phenolic derivatives may be more toxic.

The developmental/reproductive toxicity assessment cites five related studies--two on [redacted] and three on [redacted]

1. [redacted]

A teratology study of the effects of [redacted] (unstated purity) on Sprague-Dawley rats yielded increased incidences of resorptions at 10 mg/kg/d, and increased incidences of delayed ossification of portions of the calvarium (dome-like superior portion of the cranium) at 1000 mg/kg/d. The LOAEL for this study was 10 mg/kg/d; a NOAEL was not established. See Ref. 14T.

Reproductive toxicity was not observed at 100 mg [redacted]/kg/d; the data are regarded as inadequate for risk assessment purposes, however. See Ref. 15T.

2. [redacted]

Developmental and maternal toxicity were observed in a teratology study of [redacted] (Saytex 111) using Crl:COBS CD(SD)BR rats. At 10 mg/kg/d, effects included decreased fetal body weight; at 25 mg/kg/d, increased incidences of resorptions, malformations (leg bones), and delayed ossification (axial skeleton). Maternal toxicity was observed at 50 mg/kg/d. The LOAEL for the study was 10 mg/kg/d; the NOAEL was 2.5 mg/kg/d. See Ref. 16T and 17T.

3. Brominated [redacted]

Phenolic derivatives where two -Br's are replaced by -OH's might be more toxic than the parent compound; this is based on comparison between toxicity

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[15]Personal communication of D. Lai.

[16]Personal communication of L. Keifer, 8/23/89.

of [redacted] and [redacted] and possibility that hydroxyls might increase toxicity still further. (Ref: Personal communication of J. Seed, 8/21/89.)

Chronic, subchronic, and repeated dose toxicity

[redacted], the [redacted], and the phenolic derivatives are expected to produce chronic toxicity in humans; this is based on animal test data for [redacted] and [redacted]

The assessment of chronic, subchronic, and repeated dose toxicity cites ten studies--six on [redacted] five on [redacted]

1. [redacted]

A 30-day dietary study of technical grade [redacted] (77.4% deca-, 21.8% nona-, and 0.8% [redacted]) using Sprague-Dawley rats yielded increased spleen weight at 8 mg/kg/d, and liver enlargement at 80 mg/kg/d. According to the IRIS database (3-1-88 version), the LOAEL for this study is 80 mg/kg/d; the NOEL, 8 mg/kg/d. (See p.14 of Chronic/Subchronic Toxicity Evaluation.) The assessor has focused on the liver as the major organ for [redacted] toxicity. See Ref. 1T.

The RfD for chronic oral exposure to [redacted] is 0.01 mg/kg/d; this value is based on consideration of the results of Kociba et al. of 1973 and 1975 (part of Ref. 1T data), and Ref. 10T data.

2. [redacted]

A 90-day dietary study of [redacted] (purity unstated) using Charles River CD rats yielded increased liver weight and correlative microscopic hepatic lesions at the LOAEL of 10 mg/kg/d. See Ref 7T.

According to the IRIS database (3-1-88 version), a 90-day oral gavage study of technical grade[17] [redacted] using Sprague-Dawley rats yielded a NOAEL of 2.51 mg.kg.d, a LOAEL of 5.01 mg/kg/d; the RfD derived for [redacted] is 3 ug/kg/d. See Ref. 9T.

3. [redacted]

The phenolic degradation products are of concern equivalent to that for [redacted] While absorption and excretion may be greater and faster, respectively, than for the parent compound, insufficient information is available to quantitate the differences. Therefore, [redacted] is regarded as the closest available analog for toxicity assessment purposes.[18]

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[17]In this case, composition was ca. [redacted].

[18]Personal communication of V. Turner, 8/25/89.

Oncogenicity

Based on animal test data for [redacted] and PBBs, [redacted] and the [redacted] are of concern for oncogenicity. The phenolic derivatives are of lesser concern than the parent compound.

The assessment of oncogenicity cites two studies on [redacted]

1. [redacted]

NTP conducted a 2-year dietary study of [redacted] (94-97% pure) using F344/N rats and $B_6C_3F_1$ mice, and doses up to 2240 mg/kg/d for male rats and 7780 mg/kg/d for female mice (doses estimated for 50000 ppm in feed). There was "some, but not clear, evidence" of carcinogenicity in rats--increased incidences of liver neoplastic nodules (benign tumors) in dosed rats--and equivocal evidence of carcinogenicity in male mice--marginal increases of hepatocellular carcinomas and adenomas (combined), and thyroid gland tumors. (Ref: Carcinogenicity Evaluation.) See Ref. 13T. The potency factor, q_1^*, based on neoplastic nodules and carcinomas, combined, is 1.1×10^{-3} per mg/kg/d; this value, generated for PMN risk assessment purposes only, is not to be construed as representing Agency policy or position.[19]

2. [redacted]

Based on structural analogy to [redacted] are of concern for oncogenicity.

In an oral gavage study (25 weeks' dosing followed by 23 to 24 months' observation) of Firemaster FF-1 [redacted] using F344N rats, significant increases in incidences of hepatocellular carcinomas were reported for males at doses as low as 1.0 mg/kg/d, 5 days/wk. (Ref: HEED for PBBs, draft dated April 1989, citing NTP 1983 and Gupta et al. 1983b.) The q_1^* proposed for PBBs, regardless of degree of bromination, is 8.87 per mg/kg/d; this value from the draft HEED, not to be cited or quoted, is not to be construed as representing current Agency policy or position.

[redacted]

Degradation products with one or two -Br's replaced by -OH's are of lesser concern for oncogenicity than the parent compound; this perspective is based on an expectation that detoxification will be more effective for this more oxidized, more water-soluble derivative. (Ref: Personal communication of D. Lai, 8/21/89, 8/24/89.)

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[19]According to a draft CRAVE document (4/20/89 version, not final), the NTP study supports classification of [redacted] as a possible human carcinogen (class C), but does not support derivation of a potency factor for [redacted]

Environmental Effects

[redacted] itself is not regarded as an environmental toxicant, despite data suggestive of a capability for bioaccumulation; the [redacted] and the phenolic derivatives are regarded as posing serious hazards to birds and aquatic organisms, however.

The environmental toxicity assessment cites several studies on [redacted] and numerous studies on analogs of the [redacted] Assessment of the toxicity of the phenolic derivatives is based on QSARs.

1. [redacted] is not expected to be acutely or chronically toxic to aquatic organisms, or to bioconcentrate in aquatic organisms because of its low water solubility, high octanol/water partition coefficient, high molecular weight, and large (molecular) cross-sectional diameter. Acute and chronic toxicity to wild mammals and birds are expected to be low. (Ref: Environmental Effects assessment.) Despite such an argument against bioaccumulation for [redacted] DBDPO has been found in some aquatic organisms[20], e.g., mussels and bottom-feeders; this renders bioaccumulation of [redacted] a matter of some uncertainty.

2. [redacted]
2,3,7,8-tetrachlorodibenzodioxin (TCDD) has been offered as a worst-case analog for the [redacted]

The LD_{50} for 2,3,7,8-TCDD is < 1.5 ug/kg for Medaka fish embryos (Ref. 25T); the MATC (a no-effect concentration) for juvenile rainbow trout is < 0.038 ug/l (Ref. 26T). The LD_{50} for 2,3,7,8-TCDD is 15 ug/kg body weight for the Northern bobwhite, and >810 ug/kg for the ringed turtle-dove. Birds and fish exposed to levels of 2,3,7,8-TCDD on the order of micrograms/kg body weight and nanograms/liter exhibited the following: enzyme induction, wasting syndrome, and immunological, hematological, dermatological, and cardiovascular effects. Bioconcentration of [redacted] (e.g., [redacted] has been observed in aquatic organisms, including dolphins. (Ref. 29T.)

3. [redacted]
Chronic exposures to the phenolic degradation products are expected to result in bioaccumulation and lethality to aquatic organisms. Neutral organic QSARs are the basis for the predicted aquatic toxicity of the phenolic derivatives. For derivatives containing two hydroxyl groups in place of two bromine atoms, the range of predicted LC_{50}'s is as follows:

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[20]Environmental hazard assessment for the EPCRA (SARA Title, Section 313) petition to delist [redacted] (Petition #P-89-005); dated 7/14/89.

28-day fish	0.03 ug/l (ppb)
16-day daphnid	0.19 ug/l
chronic algal	0.02 ug/l

The 20-ppb water solubility (submitted) of the PMN substance would support the generation of 0.1 ppb of octabromo dihydroxy diphenylethane in the water column at depths where photohydroxylation may occur. That is, despite its tendency to adsorb to sediments likely to be beyond exposure to sunlight, the water solubility of the PMN substance is not so low that it precludes generation of lethal concentrations of the phenolic degradation products in the water column.

EEB recommends 0.1 ppb as the concentration of concern (COC) for the phenolic derivatives of P-89-867. The COC for [redacted] is 0.004 ppb--a number derived from a juvenile rainbow trout MATC for 2,3,7,8-TCDD and an assessment factor of 10.

V. EXPOSURE

(See Table 4 for a summary of worker exposures and releases to the environment.)

Manufacturing

[redacted] plans to manufacture the PMN substance at one site in Magnolia, Arkansas. The chemical reaction will be run as a closed-batch process; the product mixture will be mixed with water, stripped, stored; then separated further, dried, ground[21], and packaged.

Ten workers may be exposed during the batch process, QC sampling, packaging, and maintenance. Protective clothing and equipment include dust masks[22], eye goggles, disposable coveralls, fume hoods, and barrier handcreams. Worker exposures are not expected to exceed the following, in the absence of personal protective equipment:

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[21]These particles are expected to be too large for dermal absorption. (Ref: Personal communication of L. Keifer, 9/6/89.)

[22]This respresents an update since submission of the Standard Review Engineering Report, 8/9/89. Dust masks, 3M type 8720, will be used instead of respirators. (Ref: Personal communication of L. Lambrecht, 8/22/89.)

Inhalation[23]:	20 mg/d for 4 packaging and maintenance workers, 75-125 d/y; 2.5 mg/d for 4 batch process workers, 75-125 d/y; negligible exposures for QC personnel.
Dermal:	1300-3900 mg/d for 4-6 workers, 75-125 d/y.

Expected releases to the environment are as follows:

Air emissions[24]:	2.0 kg/site/d, 75-125 d/y
On-site landfill[25]:	1366 kg/y
Deep-well injection[26]:	20 ppb/site/d on 75-125 d/y. (Wastewater volume not provided.)[27]

Air emissions generated predicted human exposures of 6.45-10.75 mg PMN substance/y; the estimate (Generic Turner Method) describes an exposure that is 100 m downwind from the source, and 3 m high. Estimates are not available for the amount of PMN substance reaching water via air emissions.

Processing

A. Plastics

Plastics processing is the target market for 95% of the production volume for P-89-867. At [redacted] sites, the PMN substance is to be blended into plastics, extruded, pelletized, and drummed in operations that are essentially closed-system; the PMN substance would constitute [redacted] of the plastic product.

Workers may be exposed to the PMN substance during weighing and transfers. Information about protective equipment and controls is not available. Worker exposures expected are as follows, in the absence of protective equipment:

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[23]Based on monitoring data by the submitter for a similar chemical, with similar protective measures.

[24]From grinding and packaging operations. Compare this figure, a maximum of [redacted] kg/y, to [redacted] releases to air by [redacted]; in the 1987 reporting year for the Toxic Chemicals Release Inventory [redacted] reported releases of [redacted] kg/y to air by its plant in [redacted], a location about [redacted] miles from the [redacted].

[25]Dust from packaging operations.

[26]On-site injection of filtered wastewater from batch process and cleaning operations. The waste is supposed to reside at a level below the water table.

[27]20 ppb is also the water-solubility provided for the PMN substance.

Inhalation[28] : 150 mg/d for 9-30 workers, 50-125 d/y
Dermal: 1300-3900 mg/d for 9-30 workers, 50-125 d/y

Environmental releases of the PMN substance are not expected; the estimated 1000-1500 kg/y that is landfilled is regarded as encapsulated in plastic.

B. Non-consumer textiles and adhesives, and miscellaneous flame retardant applications

These markets are targeted for [redacted] of the production volume of the PMN substance. The products of this processing at [redacted] sites would be aqueous dispersions containing the PMN substance at levels of [redacted].

Workers may be exposed to the PMN substance during weighing and transfers; information about protective equipment and controls is not available. Worker exposures expected are as follows, in the absence of protective equipment:

Inhalation[25]: 150 mg/d for 15-60 workers, 50-250 d/y
Dermal: 1300-3900 mg/d for 15-60 workers, 50-250 d/y

Expected environmental releases are as follows:

Landfill: 140 kg/d

Use

A. Plastics

Plastics containing the PMN substance would be extruded, molded, and cast into objects at [redacted] sites. The PMN substance is regarded as encapsulated in plastic polymer; therefore, no worker or environmental exposures to the PMN substance are expected.

B. Non-consumer textiles and adhesives, and miscellaneous flame retardant applications

The aqueous dispersion for these applications would be used at [redacted] sites.

Workers may be exposed to the PMN substance during transfers and application; information about protective equipment and controls is not available. Inhalation exposure to the dispersed PMN substance is not expected. Worker exposures expected are as follows, in the absence of protective equipment:

Dermal: [redacted] mg/d for [redacted] workers, [redacted] d/y

[28]Based on OSHA nuisance dust standard.

Expected environmental releases are as follows:

Water: [redacted] kg/site/d for [redacted] sites, [redacted] d/y

Estimated removal of the [redacted] in wastewater treatment at POTWs is 90%. Removal rates for the phenolic derivatives are expected to be slightly higher; and for the [redacted], the same as for [redacted][29]

If fish bioaccumulate the PMN substance, and if the estimated BCF of 32000 is appropriate for the PMN substance, then releases to water would generate an estimated human exposure of 0.89-23.0 mg/y via fish ingestion.

If the PMN substance survives the processes that generate drinking water from the water-borne releases of the PMN substance, then the maximum human exposure expected due to ingestion of drinking water is 0.09 mg PMN substance/y.

VI. RISK

Approximations used in calculating risks for this case include the following: (1) Animal toxicity values from GI routes of administration are applicable to human exposures via inhalation, and the chronic oral RfD is applicable to inhalation exposure. The absorption assessment supports this approach. (2) Dermal exposure does not generate significant risk. This is based on an expectation of no dermal absorption of the PMN substance, and an acute dermal LD_{50}>2000 mg/kg. (3) Workers are exposed to the PMN substance, undegraded. (4) The general public is exposed to PMN substance, undegraded. This is a poor assumption, since degradation of the PMN substance in sunlight is expected to proceed rapidly. (5) Aquatic organisms bioaccumulate [redacted] (6) Via a combination of longevity and successive releases, the [redacted] are present in the water column at concentrations sufficient to produce the chronic effects predicted.

[29]Ref: Personal communication of A. Leifer, 8/22/89.

Workers

The risks for workers in terms of MOEs and incidence of cancer, based on analogy of [redacted] to [redacted] appear in the table below.

When based on a LOAEL or NOEL, 1000 and 100, respectively, are regarded as adequate MOEs. Therefore, the MOEs for the manufacturing and processing worker exposures via inhalation are inadequate. These worker exposures exceed the chronic oral RfD (0.01 mg/kg/d), as well.

Cancer risks of $<10^{-5}$ are regarded as not significant for workers. Based on analogy to [redacted] therefore, the cancer risks for workers are as follows: (1) significant for both groups of processing workers; (2) marginally significant for the packaging and maintenance workers in manufacturing, the $>10^{-5}$ aspect being mitigated by the fact that the q_1^* is based on a combination of benign and cancerous tumors; (3) not significant for batch workers in manufacturing.

Exposure scenario	Non-cancer risks			Cancer risk	
		MOE[a]			
	Avg. dose[b], mg/kg/d	Dev. LOAEL	Subchr. NOEL	LADD[c], mg/kg/d	Incidence of cancer
Manufacturing:					
Pkging & Maint. ([redacted] wrkrs, [redacted] d/y)	0.28 to 0.33	30	30	0.0335 to 0.0559	4×10^{-5} to 6×10^{-5}
Batch ([redacted] wrkrs, [redacted] d/y)	0.36 to 0.42	240 ~~30~~	220 ~~30~~	0.00419 to 0.00699	5×10^{-6} to 8×10^{-6}
Processing:					
Plastics [redacted] wrkrs, [redacted] d/y)	2.1 to 2.5	4	4	0.168 to 0.419	2×10^{-4} to 5×10^{-4}
Textiles, etc. [redacted] wrkrs, [redacted] d/y)	2.1 to 2.5	4	4	0.168 to 0.839	2×10^{-4} to 9×10^{-4}

Footnotes:

[a]Margin of Exposure = (LOAEL or NOEL)/(Avg. dose)

[b]Avg. dose in mg/kg/d = (Avg. mg/d/person) x (1/avg. adult human wt.), where avg. adult human wt. is 60 kg for females, 70 kg for males.

[c]LADD, Lifetime Average Daily Dose = [redacted]

General Public

The risks for the general public in terms of MOEs and incidence of cancer, based on analogy of [redacted] to [redacted] appear in the table below. Exposures arising from manufacturing emissions to air, ingestion of fish that might have bioaccumulated [redacted] and ingestion of water are not expected to generate cancer, developmental toxicity, or subchronic toxicity risks that are unacceptable for the general public. In addition, the chronic oral RfD is not exceeded.

Exposure scenario	Avg. dose x 10^4, mg/kg/d	MOE Dev. LOAEL	MOE Subchr. NOEL	Cancer
Fish ingestion	0.42 to 9.0	>1000	>1000	$4x10^{-8}$ to $1x10^{-6}$
Drinking water ingestion	0.035	>1000	>1000	$4x10^{-9}$
Air emissions from mfg	2.5 to 4.2	>1000	>1000	$3x10^{-7}$ to $5x10^{-7}$

Environment

Because of the considerable uncertainty about the environmental fate of the PMN substance, the relevance of the risks presented in this section is highly conjectural.

Risk to aquatic organisms generated by the phenolic degradation products was addressed via an SIC code-based version of PDM3, the probabilistic dilution model. The following SIC codes were used in arriving at this result: 2891- Adhesives and Sealants Manufacture; 2821, 2823, 2824- Plastic Resins & Synthetic Fiber Manufacture; 4952- POTW (Industrial, includes POTWs that receive industrial discharges).

The COC of 0.1 ppb would be exceeded on [redacted] sites for the non-consumer textile etc. use when all of the [redacted] degrades to octabromo phenolic products. No correction has been pursued for degradation of the parent compound to products other than the subject phenolic product.

Insufficient information is available to describe risk to aquatic organisms arising from the following: (1) bioaccumulation of [redacted] or its degradation products from sediments and/or the water column; and (2) lesser-brominated [redacted] reaching water via air.

VII. TEST RECOMMENDATIONS

Testing is supportable on a may-present basis--developmental toxicity, subchronic toxicity, oncogenicity, aquatic toxicity--, as well as on an exposure basis (production volume >100,000 kg/y). The following tests are recommended:

Health effects:

- o Standard teratology study using Sprague-Dawley rats as one of the two test species.
- o 90-day subchronic toxicity test using Sprague-Dawley rats as one of the test species.
- o Observation of liver toxicity in the subchronic study is the proposed basis for recommendation of a 2-year cancer bioassay (oral route) in Sprague-Dawley rats.

Note that test animals species selected, endpoints examined, and purity of the test article appear to have affected observation of toxicity in the case of the [redacted] analog.

Environmental Fate:

- o Photolysis in water, with sampling every hour and C^{13} NMR identification and quantitation of reactant and product chemical species with time. The intent is to determine rates of degradation and relative ratios of [redacted] and products versus time.
- o Photolysis in air of varied humidity; intent is same as for photolysis in water.
- o Conduct realistic environmental fate studies using guidelines provided by the Exposure Evaluation Division/OTS.

Environmental Effects:

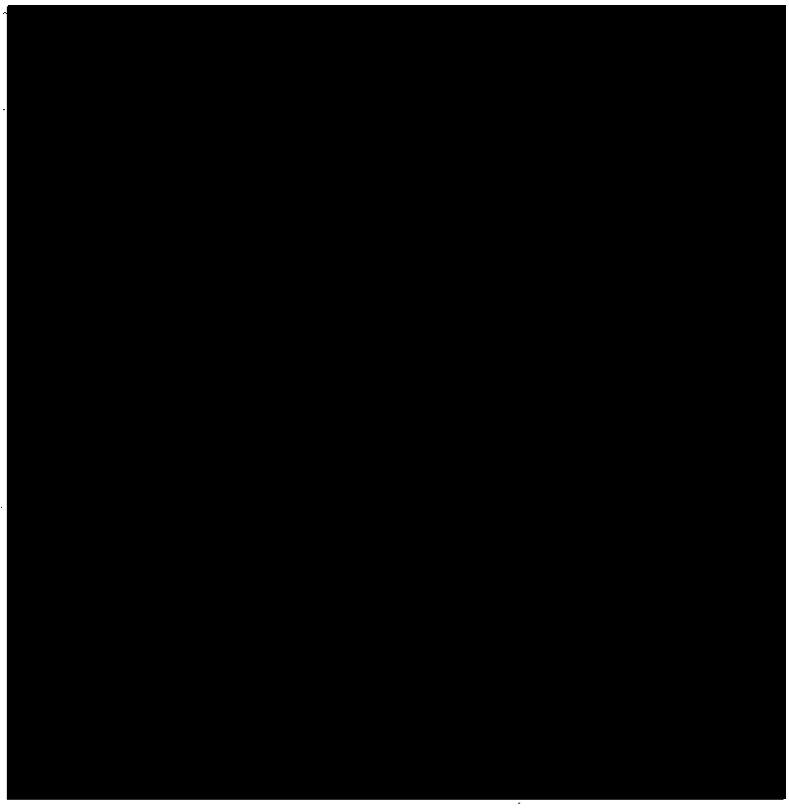
For the parent compound (exposure-based case):

- o Bioaccumulation in fish and oysters.
- o 60-d fish test.
- o Chronic algal toxicity test.
- o Chronic daphnid toxicity test.
- o Tadpole/sediment subchronic test (Test Standard #795.145) (a 30-day test).
- o Chironamid (bloodworm) sediment invertebrate test (Test Standard #795.135).

For degradation products (may-present case):

- o The results of the environmental fate testing may preclude or suggest aquatic toxicity testing of degradation products.

Figure 1: Chemical Structures



P-89-867
[redacted]
1,2-bis(pentabromodiphenyl)ethane
CAS # 84852-53-9

[redacted]
(analog)

[redacted]

[redacted]

X+Y=8, m+n=2

(Table 1)

(Petition # [redacted] , [redacted] (7/12/89)

(Table 1:) Lowest concentrations at which adverse effects were observed
(Reference numbers are from Table 2.)

Effect	DBDPE	Effect value [redacted]	[redacted]
Developmental toxicity	LOAEL: 10 mg/kg/d, NOAEL: Not established. (Ref. 14T.)	LOAEL: 10 mg/kg/d, NOAEL: 2.5 mg/kg/d. (Ref. 17T.)	1 ug/kg/d for 2,3,4,7,8-[redacted] (Ref. 19T.)
Reproductive toxicity	(See Ref. 15T.)	-	-
Maternal toxicity	-	50 mg/kg/d (Ref. 16T, 18T.)	3 ug/kg/d (Ref. 19T.)
Repeated-dose toxicity	LOAEL as 80 mg/kg/d, NOAEL as 8 mg/kg/d. (Ref. 1T.)	(See Ref. 8T.)	-
Subchronic toxicity	-	LOAEL: 10 mg/kg/d, NOEL: not established. (Ref. 7T.)	-
Chronic toxicity	Male rats- LOAEL: 2240 mg/kg/d, NOEL: 1120 mg/kg/d. Male mice- NOEL: <3200 mg/kg/d. (Ref. 11T.)	-	-
Oncogenicity	Limited evidence of carcinogenicity (Ref. 13T.)	-	-
Ecotoxicity	Not expected (Ref. 21T, 22T, 23T, 24T.)	NOEC as < 0.038 ug/l, based on analogy to [redacted]. (Ref. 26T.)	Same as for [redacted]

(From Petition [redacted] P-89-867 Table 2

(From Petition [redacted] P-89-867 Table 3)

(Table 2:) Synopses of studies cited in health and environmental effects evaluations for Petition [redacted]

Table 2: Synopses of studies cited in health and environmental effects evaluations for Petition [redacted]

Ref. #	Reference	Test article	Test animals	Test	Doses	Effects	Comments
Repeated-dose, Subchronic, and Chronic toxicity							
1	Norris et al. 1973 and 1975 Sparschu et al. 1971	77.6% 21.8% 0.8% [redacted]	5 males/dose Sprague-Dawley rats	30-day dietary	ca. 0, 8, 80, 800 mg/kg/d (0, 0.1, 1, 10 ppm in feed)	LOAEL: 80 mg/kg/d, liver enlargement NOEL: 8 mg/kg/d	Small group size, single sex, absence of clinical chemistry and microscopic examination, limited number of tissues examined. The effect values are from the IRIS database (3-1-88 version), which apparently did not consider the Sparschu data on spleen weights. (See p.14 of chronic/subchronic toxicity evaluation.) Significantly-increased spleen weights were reported in the 8-mg/kg/d test animals.
2	Attachment 1 of assessor's [redacted]	[redacted] purity unstated	100/sex/dose Charles River CD rats	28-d dietary	ca. 0, 10, 100 mg/kg/d (0, 100, 1000 ppm in feed)	NOAEL: > 100 mg/kg/d	
3	NTP 1986	99% [redacted]	5/sex/species/dose F344/N rats and B6C3F1 mice	14-d dietary	ca. 0, 225, 450, 900, 2240, and 4480 mg/kg/d for male rats; ca. 0, 778, 1556, 3112, 7780, 15560 mg/kg/d for female mice (Calculations based on 2-year companion study) (0, 5000, 10000, 20000, and 100000 ppm in feed)	NOAEL: > highest doses	No data on organ weights, hematology, clinical chemistry, histopathology.
4	NTP 1986	96-99% [redacted]	10/sex/species/dose F344/N rats and B6C3F1 mice	13-week dietary	ca. 0, 140, 280, 560, 1120, and 2240 mg/kg/d for male rats; ca. 0, 470, 940, 1880, 3760, and 7780 mg/kg/d for female mice (0, 3100, 6200, 12500, 25000, and 50000 ppm in feed)	NOEL: > highest doses for each sex and species	No data on organ weights, hematology, or clinical chemistry.
5	Attachment 1 of assessor's [redacted]	[redacted] purity unstated	10/sex/dose Charles River CD rats	28-d dietary	ca. 0, 10, 100 mg/kg/d (0, 100, 1000 ppm in feed)	LOAEL: 10 mg/kg/d, increased liver weight, liver lesions NOEL: Not attained	Absence of experimental data and complete protocol for evaluating results fully.
6	See ref. 5.	See ref. 5.	See ref. 5.	See ref. 5.	ca. 0, 10, 100, 1000 mg/kg/d (0, 100, 1000, 10000 ppm in feed)	LOAEL: 10 mg/kg/d, liver lesions NOEL: Not attained	See ref. 5.

(From Petition [redacted])

P-89-867

Table 2, continued

(Table 2, continued)

7	See ref. 5.	See ref. 5.	35/sex/dose Charles River CD rats	90-day dietary	See ref. 6.	LOAEL: 10 mg/kg/d, increased liver weight and correlative microscopic hepatic lesions NOEL: Not attained	See ref. 5.
8	[redacted]sor's	[redacted] purity unstated, micronized dust	Charles River CD rats	Inhalation, 8 h/d, 14 consecutive days, whole-body exposure	Nominally 1.2, 12, 120, and 1200 mg/cm air; Crude estimates of doses are 0.14, 1.4, 14, 140 mg dust/kg body wt./d	LOAEL: 1.4 mg/kg/d, increased liver weight, microscopic liver lesions NOEL: 0.14 mg/kg/d	Measured concentrations in air were 15 to 45% of nominal. % of particles in respirable size range not provided. Oral exposures likely due to ingestion by preening.
9	Carlson, 1980	Technical grade OBDPE: 30.7% 45.1% 13 % 8.5% 1.6% 1.1% [redacted]	6 males/dose Sprague-Dawley rats	90-d oral gavage (administered in corn oil)	0, 0.625, 1.25, 2.51, 5.01, 10.02, and 20.04 mg/kg/d	LOAEL: 5.01 mg/kg/d (See comments.) NOAEL: 2.51 mg.kg/d	According to IRIS database (3/1/88 version), the three highest doses should be regarded as possible adverse effect levels because no histologic evaluations were done on those groups of animals. Liver enzyme induction was reported for all dose levels; this is not considered adverse in absence of a histopathology evaluation.
10	Kociba et al. 1975	77.4% 21.8% 0.8% [redacted]	25/sex/dose Sprague-Dawley (Spartan) rats	2-y dietary	0, 0.1, 1 mg/kg/d	LOAEL: Not attained NOEL: 1 mg/kg/d (See comments.)	IRIS database (3/1/88 version) concludes that NOEL is 1 mg/kg/d.
11	NTP 1986	94-97% [redacted]	50 /sex/species/dose F344/N rats and B6C3F1 mice	2-y dietary	0, 1120, and 2240 mg/kg/d for male rats; 0, 3760, and 7780 mg/kg/d for female mice (0, 25000, and 50000 ppm in feed)	LOAEL: 2240 mg/kg/d in male rats, increased incidences of liver thrombosis and degeneration, spleen fibrosis, forestomach acanthosis, lymphoid hyperplasia; 3200 mg/kg/d in male mice. NOEL: 1120 mg/kg/d in male rats, >2550 mg/kg/d in female rats; >7780 mg/kg/d in female mice, not achieved in male mice.	No data on organ weights, hematology, and clinical chemistry.
Oncogenicity							
12	See ref. 10.	See ref. 10.	See ref. 10.	See ref. 10.	See ref. 10.	No treatment-related neoplastic or non-neoplastic lesions.	
13	See ref. 11.	See ref. 11.	See ref. 11.	See ref. 11.	See ref. 11.	Rats: Significantly increased incidences of liver neoplastic nodules (benign tumors) in dosed males and females; incidence of hepatocellular carcinomas (malignant tumors) was low in all groups and was not compound-related. Regarded as some evidence of carcinogenicity. Mice: Marginal increases in hepatocellular adenomas and carcinomas (combined) and thyroid gland tumors in males were regarded as equivocal evidence of carcinogenicity. No treatment-related lesions were reported for female mice.	

Table 2, continued

(Table 2, continued)

Developmental, Reproductive, and Maternal Toxicity

14	Morris et al, 1975. [redacted]	[redacted] 6-10 Br/molecule, purity unstated	20/dose Presumed pregnant Sprague-Dawley rats (Spartan strain)	Oral teratology with intubation on gestation days 6-15, sacrifice on gestation day 21.	0, 10, 100, 1000 mg/kg/d in corn oil	LOAEL: 10 mg/kg/d, fetal effects and resorptions. NOAEL: Not established	At 1000 mg/kg/d, there were increased incidences of subcutaneous edema and delayed ossification of portions of the calvarium. (Raw submitted summary tables, but no raw data, to support its contention that historical controls should be used instead of the test controls, and that no adverse effects were observed at 1000 mg/kg/d.
15	Morris et al, 1975.	See ref. 14.	See ref/ 16.	Single-generation reproduction: 90-day dietary administration before and throughout mating, gestation, and lactation.	0, 3, 30, and 100 mg/kg/d	No adverse effects on female reproductive performance reported.	Summary of data was basis of review. There was no examination of uterus for implantation sites; it is possible to find a statistically significant increase in resorption in the absence of a statistically significant decrease in litter size.
16	Lochry and Christian, 1985	[redacted] Saytex 111	Presumed pregnant rats	Pilot range-finding teratology study, with oral gavage on gestation days 6-15	0, 5, 25, 50, 75, 100, 500, 2500, and 5000 mg/kg/d in corn oil	At 50 mg/kg/d, total resorption of litters. At 75 mg/kg/d, body weight gain. (Maternal toxicity)	
17	See ref. 16. By Argus Research Labs under contract [redacted]	See ref. 16.	25/dose Presumed pregnant Crl:CD®S CD(SD)BR rats	Teratology study, with oral gavage on gestation days 6-15, sacrifice on day 20.	0, 2.5, 10, 25 mg/kg/d in corn oil	LOEL: 10 mg/kg/d, decrease in fetal body weight NOEL: 2.5 mg/kg/d	At 25 mg/kg/d, increase in resorptions/litter, increase in number of litters with resorptions, increase in structural malformations (leg bones, axial skeleton), and delayed ossification.
18	Letter from [redacted]	DBDPE-DE-79, purity unstated		"preliminary tests"		At 50 mg/kg/d, fetal abnormalities and embryo/fetal deaths.	Submitter attributed adverse effects to maternal toxicity.

(Table 2, continued)

19	Birnbaum, Harris, Barnhart, Morrissey, 1987	[redacted]	Pregnant C57BL/6N mice	Gavage on gestation days 10-15, necropsy on gestation day 18.	For A: 0, 1, 3, 10, 20, 30, 40, 60, 80 ug/kg/d	For A: Maternal tox.: At 3 ug/kg, decreased weight gain, increased liver weight. Developmental tox.: At 1 ug/kg, hydronephrosis; at 30 ug/kg, cleft palate.	Similar effects for B and C; but C is one fourth as potent as A, and B is one tenth as potent as A.
20	Birnbaum, Harris, Crawford, Morrissey, 1987	[redacted]	Pregnant mice	See ref. 19.	A: 0-30 ug/kg, B: 0-300 ug/kg, and combinations of A and B.	Results similar to ref. 19, but combinations of A and B were additive for both cleft palate and hydronephrosis.	
Ecotoxicity							
21	Walsh et al, 1987	[redacted]	Marine algae	4-d algal growth inhibition	1 mg/l	Growth inhibition < 50%	Data questionable. Tested at concentration ca. 1000 times water solubility of [redacted]
22	Norris et al, 1974	[redacted]E	Rainbow trout	48-h bioconcentration	20 ppb in test medium	6 ppb in fish after 48 h	For a high-log P chemical, test is too short to achieve equilibrium partitioning between aqueous environment and fish.
23	Norris et al, 1973	[redacted]E	Rats	Oral LD50	-	Oral LD50 > 2 g/kg	Based on this result, not expected to be toxic to birds and wild mammals.
24	Opperhuizen et al, 1985	[redacted]	-	Bioconcentration	-	A: Bioaccumulation, cross-sectional diameter of 8.7 A B: No bioaccumulation, cross-sectional diameter of 9.6 A	Cross-sectional diameter of BDBPE believed to be much greater than that for [redacted]ne of PBDPE expected, however, since [redacted]ed in fat of some aquatic organisms.
25	Poland and Knutson, 1982	[redacted]	Medaka fish embryos		-	LD50 < 1.5 ug/kg	
26	McCinnell et al, 1987	[redacted]	Juvenile rainbow trout	28-d survival and growth	-	MATC < 0.038 ug/l	An MATC is a no-effect concentration.
27	Cooper, 1989	[redacted]	Birds and fish	-	On order of micrograms/kg body weight, and nanograms/liter	Enzyme induction, wasting syndrome, and immunological, dermatological, hepatic, hematological, and cardiovascular effects.	
28	Muir et al, 1985	Hexa- and octachloro dibenzodioxins	Rainbow trout and fathead minnow	Bioconcentration	-	Bioconcentration factor > 1000	
29	EPA Duluth, 1988 unpublished data	PentabromoDPEs	Dolphins	-	-	Evidence of bioconcentration-PBDFs found at levels of at levels of 100 to 200 ppm in dolphin tissue	The dead dolphins were found washed ashore on the East Coast of the U.S.

Table 4: Summary of worker exposures and releases to the environment

	Manufacture	PLASTICS Process #1	PLASTICS Use #1	Non-consumer textiles & adhesives, misc. flm.ret. uses Process #2	Non-consumer textiles & adhesives, misc. flm.ret. uses Use #2
# of sites	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
# of worker exposed	[redacted]	[redacted]	none	[redacted]	[redacted]
Protective equipment	barrier cream disposable coveralls dust masks goggles	unknown	none	unknown	unknown
# of days/y	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhalation exposure	[redacted] workers at 20 mg/day [redacted] workers at 2.5 mg/day [redacted] workers at neg. amts.	[redacted] workers at 150 mg/d	none	[redacted] workers at 150 mg/day	negligible
Dermal exposure	[redacted] workers at 1300-3900 mg/day	[redacted] workers at 1300 - 3900 mg/day	none	[redacted] workers at 1300-3900 mg/day	[redacted] workers at 39-117 mg/day
Enviro. releases	2.0 kg/site/d over 75-125 days/yr to air	1000 - 1500 kg/yr to landfill	none	140 kg/yr to landfill	0.1 - 0.2 kg/site/da over 25 - 250 days/y to water

(Modified from Engineering report.)